Hundred and Twenty Dollars ($920.00) to cover the extension fee as required by 37 C.F.R. §§ 1.17(a)(3) and 1.136(a).

REMARKS

I. Claim objections and claim rejections under 35 U.S.C. § 112

Claims 11-20 are objected to under 37 C.F.R. § 1.75(c) as allegedly being in improper form because a multiple dependent claim cannot depend upon another multiple dependent claim. Claims 1, 10, 12, 14, and 15 are rejected under 35 U.S.C. § 112, second paragraph, as allegedly being indefinite.

A Preliminary Amendment was filed on March 1, 2002, that is, before the April 25, 2002 mailing date of the Office Action. The Preliminary Amendment would have obviated the claim objections and the rejection under §112. However, the Preliminary Amendment apparently was not before the Examiner when the Office Action was prepared and mailed. When the situation was brought to the Examiner's attention by telephone, the Examiner recommended that Applicant should submit a copy of the Preliminary Amendment when responding to the outstanding Office Action.

In accordance with the Examiner's recommendation, Applicant is providing a copy of the Preliminary Amendment, as well as a copy of the facsimile transmission report and a copy of the PTO "Auto-Reply Facsimile Transmission" evidencing successful receipt of the Preliminary Amendment by the PTO. Entry of the Preliminary Amendment and withdrawal of the claim objections under 37 C.F.R. § 1.75(c) and the claim rejections under 35 U.S.C. § 112, second paragraph, are respectfully requested.

II. The claimed invention

The claimed invention is directed to a method for the preparation of homogeneous microparticles comprising a pharmaceutically active substance and a polymer. The pharmaceutically active substance and the polymer are suspended, dissolved, or emulsified in a solvent. The resultant suspension/solution/emulsion is atomized into droplets and then frozen. The frozen solvent is removed from the frozen droplets by sublimation, yielding dry, homogeneous microparticles.

Advantageously, the homogenous microparticles obtained with the claimed method are characterized by a ***small pore size, low friability, and a high content of the pharmaceutically active substance*** (See page 6, lines 16-25) It was unexpectedly discovered that the success in obtaining stronger microparticles, i.e., microparticles having low porosity and low friability, depends on the volume fraction of dry materials and the amount of polymer binder (See page 7, lines 11-14). In accordance with the claimed invention, therefore, the minimum dry content of the suspension/solution/emulsion from which the droplets are formed is 15% by volume and the polymer binder content is at least 5%. The claimed microparticles having a low friability can withstand coating with a polymeric film. Furthermore, a content up to 95% by weight of the active ingredient is possible.

Accordingly, the claimed invention overcomes the disadvantageous practice of the prior art of increasing particle durability by increasing particle density.

III. Prior art rejections- US 5,017,383 to Ozawa et al.

A. Rejection under §102(b)

Claims 1-20 are rejected under 35 U.S.C. § 102(b) as allegedly being anticipated by US 5,017,383 to Ozawa et al. ("Ozawa"). The Examiner alleges that Ozawa teaches the claimed method and microparticles.

Anticipation requires that each and every feature of the claimed invention be disclosed in a single prior art reference. Applicant submits that the claimed invention is not disclosed by Ozawa. For example, Ozawa does not disclose the sublimation step of the claimed invention and, therefore, the claimed method and microparticles are not anticipated by Ozawa.

Specifically, Applicant's invention requires that solvent be removed from the *frozen* particles by sublimation. Sublimation is defined as "the process by which solids are transformed directly to the vapor state or vice versa without passing through the liquid state" (McGraw-Hill Dictionary of Scientific and Technical Terms, 2nd Ed., 1978). Therefore, the frozen solvent is removed from the frozen particles without ever becoming a liquid.

Ozawa discloses a process for producing a fine coated pharmaceutical preparation. The process involves forming frozen particles of a liquid medium containing a dissolved or suspended drug, classifying the frozen particles, and mixing an isolated fraction of the particles with a coating material. The temperature of the coated frozen particles is then increased to melt and liquefy the liquid medium. The liquid medium is thereby removed from the particles. In other words, Ozawa *requires* that the temperature of the frozen coated particles be raised to above the melting point of the liquid medium. As such, the liquid medium is therefore in the liquid state while being removed from the coated particles.

In contrast to Ozawa and in accordance with the claimed invention, the solvent in the frozen particles is removed by sublimation, that is, while the particle are in a frozen state. In no instance does the solvent become liquid when being removed. In addition, the claimed invention requires that the droplets of the liquid medium have a minimum dry content of 15%, and that the polymer be present in a amount of at least 5% by weight of the dry content of the medium. These features of the claimed invention are not disclosed by Ozawa.

For all of the foregoing reasons, the claimed invention is not anticipated by Ozawa. Withdrawal of the rejection of claims 1-20 is requested.

With specific regard to product-by-process claims 18 and 19, the Examiner alleges that Ozawa anticipates claim 18 by teaching a microparticle, and claim 19 by teaching a coated microparticle. In essence, the Examiner alleges that the product obtained according to the claimed method is the same as the product prepared in accordance with Ozawa.

Applicant submits that the product obtained with the claimed method is structurally distinguishable over the product obtained by Ozawa. The claimed microparticles are characterized by a small pore size and low friability which is attributable, in part, to (1) a sublimation step that is not disclosed by Ozawa, and (2) the recited volume fraction of dry materials and the amount of polymer binders that are not disclosed by Ozawa. As disclosed on page 7, lines 19-23 of the specification, the structure of the suspension/solution/emulsion is retained in the frozen droplets even after the frozen liquid is sublimated due to a lack of migration of the substances during drying. In contrast, Ozawa expressly requires the application of heat to the formed microparticles. As such, the structure of the claimed microparticles of the claimed invention must be different and are not, therefore, anticipated by Ozawa. Thus, withdrawal of the §102 rejection of claims 18 and 19 in view of Ozawa is requested.

B. Rejection under §103(a)

Claims 1-20 are rejected under 35 U.S.C. § 103(a) as allegedly being unpatentable over Ozawa. Applicant submits that the remarks in Section A, above, in regard to the rejection under §102(b), are applicable, and, therefore, responsive to the rejection under §103(a). In brief, Ozawa discloses a process for preparing particles in which frozen microdroplets comprising a liquid medium are covered with a coating mixture. The microparticles are allowed to melt and liquefy. The liquid medium is removed from the particles in the form of a *liquid*.

In contrast to Ozawa and in accordance with the claimed invention, solvent is removed from the frozen particles by sublimation, e.g., freeze drying. There is no suggestion in Ozawa that freeze drying could be successfully used to remove the solvent, and in fact, the use of freeze drying is antithetical to Ozawa, as Ozawa explicitly requires that the liquid medium be removed while its temperature is above its freezing (melting) point. Therefore, freeze drying could not be used without destroying the method of Ozawa.

In addition, the data provided at pages 12-15 of the specification shows that microparticles prepared by the claimed method are characterized by a small pore size and advantageous mechanical properties. Table 2 at page 15 of the specification indicates that the claimed microparticles (sieve fraction: 450-630 μm) had a small pore size (pore median size: 0.0005-10 μm) and began to deform at a pressure of 94 kPa (13 psi). These advantages are attributable to the recited volume fraction of dry materials and the amount of polymer binders as well as the sublimation step which does not disrupt the structure of the droplets due to a lack of migration of substances during drying.

There is no disclosure by Ozawa that the prior art method yields particles having comparable low friability. Withdrawal of the rejection of claims 1-20 under §103(a) in view of Ozawa is respectfully requested.

IV. Prior art rejections- GB 2,329,124 to Ratwatte

A. Rejection under §102(b)

Claim 1 is rejected as allegedly being anticipated by GB 2,329,124 to Ratwatte ("Ratwatte"). Ratwatte discloses and claims a method wherein an agent composition is dispersed in a solution of a coating material in a liquid carrier material to form a dispersed mixture which is then sprayed to form droplets of the dispersed mixture. The droplets are frozen and dried to produce a plurality of coated individual particles. It is the Examiner's position that the components and steps of the claimed method read upon Ratwatte's disclosure.

The Examiner acknowledges that Ratwatte does not disclose the percentages of the components of the starting materials. Applicants submits that the recited volume fraction of dry materials and the amount of polymer binders are essential to obtain the claimed microparticles and advantageous properties, i.e., small pore size, low friability, and a high content of the pharmaceutically active substance. Therefore, in view of the absence of any meaningful disclosure or guidance by Ratwatte with respect to the percentages of the components, it is submitted that Ratwatte does not describe the claimed invention sufficiently to have placed the person of ordinary skill in the art in possession of it.

If, for the sake of argument, it is deemed that Ratwatte is enabling, to which Applicant does not agree, Ratwatte discloses at best a broad genus for the preparation of microparticles that, in the Examiner's opinion, appears to encompass the species of the claimed invention.

However, as previously mentioned, Ratwatte differs from the claimed invention in that the recited minimum dry content and polymer binder content are not disclosed. Specifically, in accordance with the claimed invention, the minimum dry content of the suspension/solution/emulsion from which the droplets are formed is 15% by volume and the polymer binder content is at least 5%.

Thus, the genus allegedly disclosed by Ratwatte does not anticipate the species of the claimed invention. In this regard, the Examiner's attention is directed to the discussion appearing in Chisum on Patents, Chapter 3, Novelty, §3.02[2] - Genus and Species - Combination ("Chisum"), and the cited cases which support the novelty of the claimed invention in view of Ratwatte. Specifically, the relevant law is summarized by Chisum as follows:

> It is well settled that a valid patent may issue for a nonobvious improvement on a prior patented invention, even though the improvement falls within the claims of that prior patent. This suggests that ***a prior genus which does not explicitly disclose a species does not anticipate a later claim to that species***. The genus, if later, would not infringe the species claim, at least not in all cases. Hence, it does not anticipate. (Citations omitted).

Accordingly, it is respectfully submitted that Ratwatte does not anticipate the alleged species represented by claim 1. For the same reasons, Ratwatte does not anticipate the alleged species represented by product-by-process claims 18 and 19. By their direct dependence on claim 1, the microparticles of claims 18 and 19 are obtained when the dry content of the liquid medium is at least 15% by volume and the polymer binder content is 5% by weight. This species is not explicitly disclosed by Ratwatte.

For all of the foregoing reasons, withdrawal of the §102 rejection of claims 1, 18 and 19 in view of Ratwatte is requested.

B. Rejection under §103(a)

Claims 1-20 are rejected under 35 U.S.C. § 103(a) as allegedly being unpatentable over Ratwatte. The Examiner acknowledges that Ratwatte does not specifically teach Applicant's claimed polymers, does not give percentages of the individual components of the composition, and does not specify the particular solvents claimed by Applicant. Nevertheless, the Examiner alleges that Ratwatte suggests the claimed method and microparticles.

Applicant agrees with the Examiner that Ratwatte neither discloses nor suggests that improved microparticles comprising a pharmaceutically active agent could be prepared by atomizing a liquid medium having a minimum dry content of 15% and comprising the active agent and at least 5% by weight of a binder polymer. These percentages are essential to obtain the advantageous mechanical properties reported in Table 2 on page 15 of the specification as well as the ability to achieve a content of the active ingredient as high as 95%.

In view of the lack of any meaningful disclosure, it is clear that Ratwatte fails to appreciate the significance of the respective percentage of the dry content and polymer binder in the preparation of microparticles. Accordingly, at the time the claimed invention was made, Ratwatte would have provided no motivation to persons in the art to apply their skills to seek a method of preparing and improving the mechanical properties of microparticles comprising a pharmaceutically active substance. Therefore, Applicant submits that the claimed invention represents an unexpected improvement over the prior art. The success in obtaining particles having a small pore size, low friability and advantageous mechanical properties depends on the recited volume fraction of dry material and the amount of polymer binder. Accordingly, withdrawal of the rejection of claims 1-20 under §103(a) in view of Ratwatte is respectfully requested.

CONCLUSION

Upon entry of this Letter, claims 1-23 remain pending. Applicant respectfully submits that claims 1-23 are directed to patentable subject matter. Accordingly, Applicant requests allowance of the claims.

Authorization is hereby given to charge any fee in connection with this communication to Deposit Account No. 23-1703.

Dated: Oct 25, 2002

Respectfully submitted,

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Attachments: Preliminary Amendment filed March 1, 2002
Facsimile transmission report dated March 1, 2002
PTO "Auto-Reply Facsimile Transmission" dated March 1, 2002